NIH-Industry Program: New Therapeutic Uses for Existing Agents

WEBINAR
MAY 29, 2014

NCATS

NIH National Center for Advancing Translational Sciences

Webinar Contents

- Overview of the program
- Accessing Agent information
- X02 application content
- X02 evaluation
- Contact with companies and template agreements
- UH application process
- UH application content
- Governance
- Frequently asked questions
- Open questions

How to submit questions

- Questions may be submitted anytime during the webinar
- Please submit questions using the chat feature of the webinar
- Your questions will only be visible to the webinar moderators at NIH

NCATS: New Therapeutic Uses (NTU) Program

Goal:
To identify new therapeutic uses of proprietary Agents across a broad range of human diseases in areas of medical need.

The pilot initiative demonstrated:

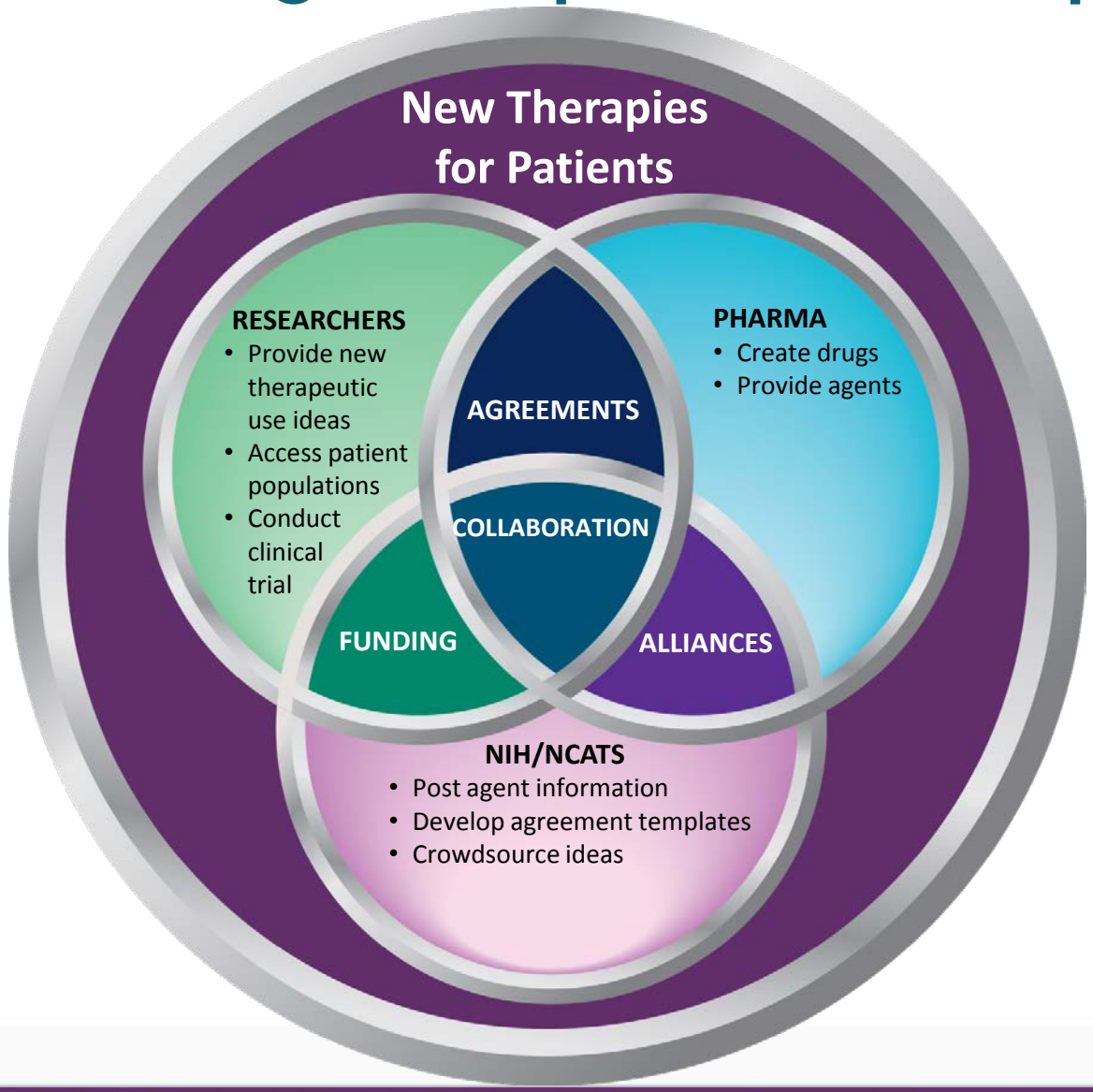
- High levels of enthusiasm for the program by the Research Community and Pharmaceutical Companies
- Pharmaceutical-Academic collaborations could be established on a tight timeline and Template Agreements facilitated this process
- The awarded projects are proceeding on target

NCATS: NTU Program

The current initiative:

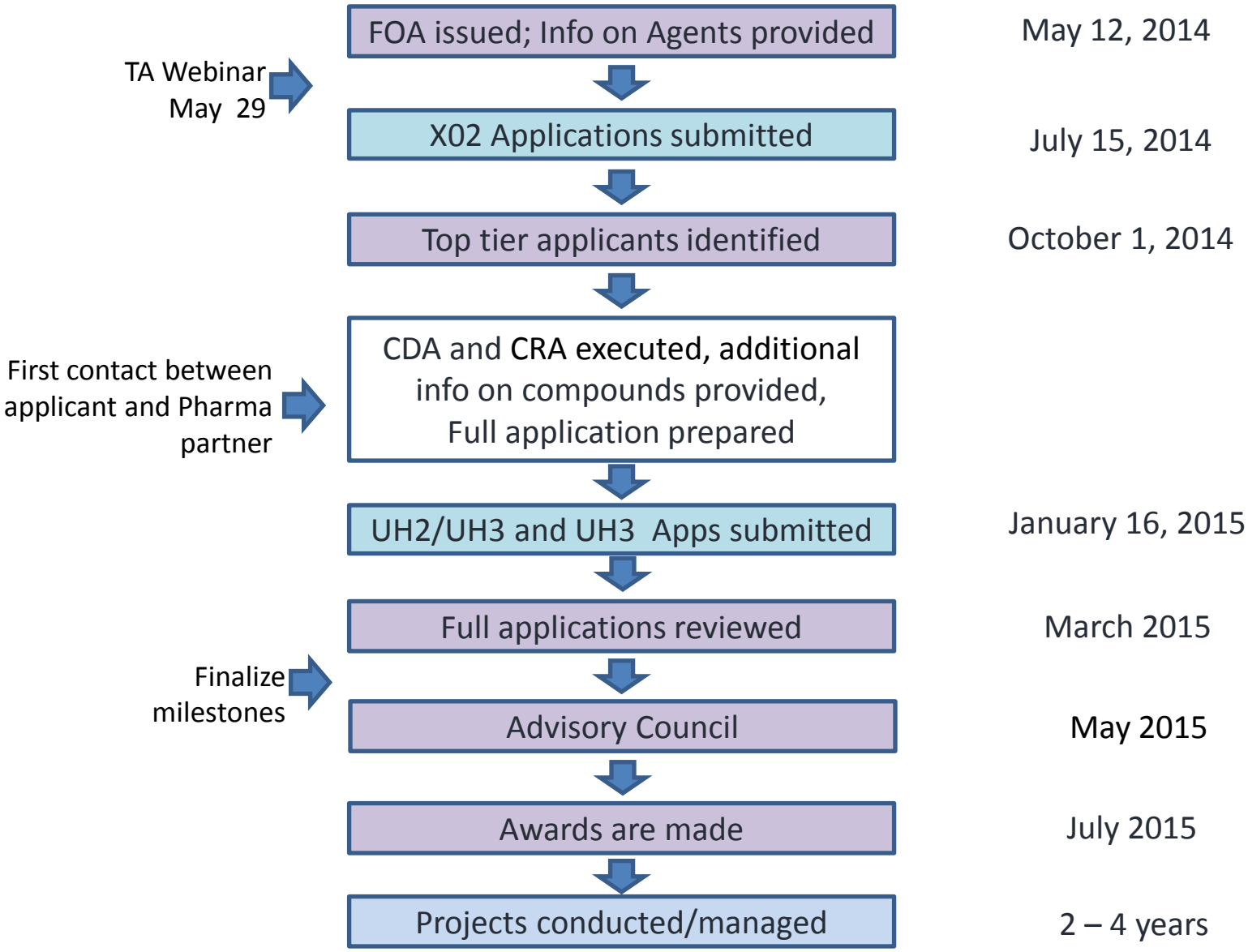
- Allows investigators to propose new therapeutic uses for Agents from pharmaceutical company partners across a broad range of human diseases
- Expands the program to include pediatric indications
  - **NIH provides:** template partnership (confidential disclosure and collaborative research) agreements, review, funding, and oversight
  - **Pharmaceutical partners provide:** Agents, in kind support, and pertinent data
  - **Academic researchers provide:** deep understanding of disease biology, new concepts to test, and access to patients

Accelerating Therapeutic Development



Agents: Criteria for selection

- Mechanism of action for each Agent must be known and selective
- Pharmacokinetics are suitable to explore the mechanism in a new indication
- Phase 1 clinical trial has been completed
- Safety profile is understood
- Pre-clinical and clinical Agent and placebo will be provided for studies
- Availability of data/information for regulatory documents to enable an investigator to file an Investigational New Drug (IND) application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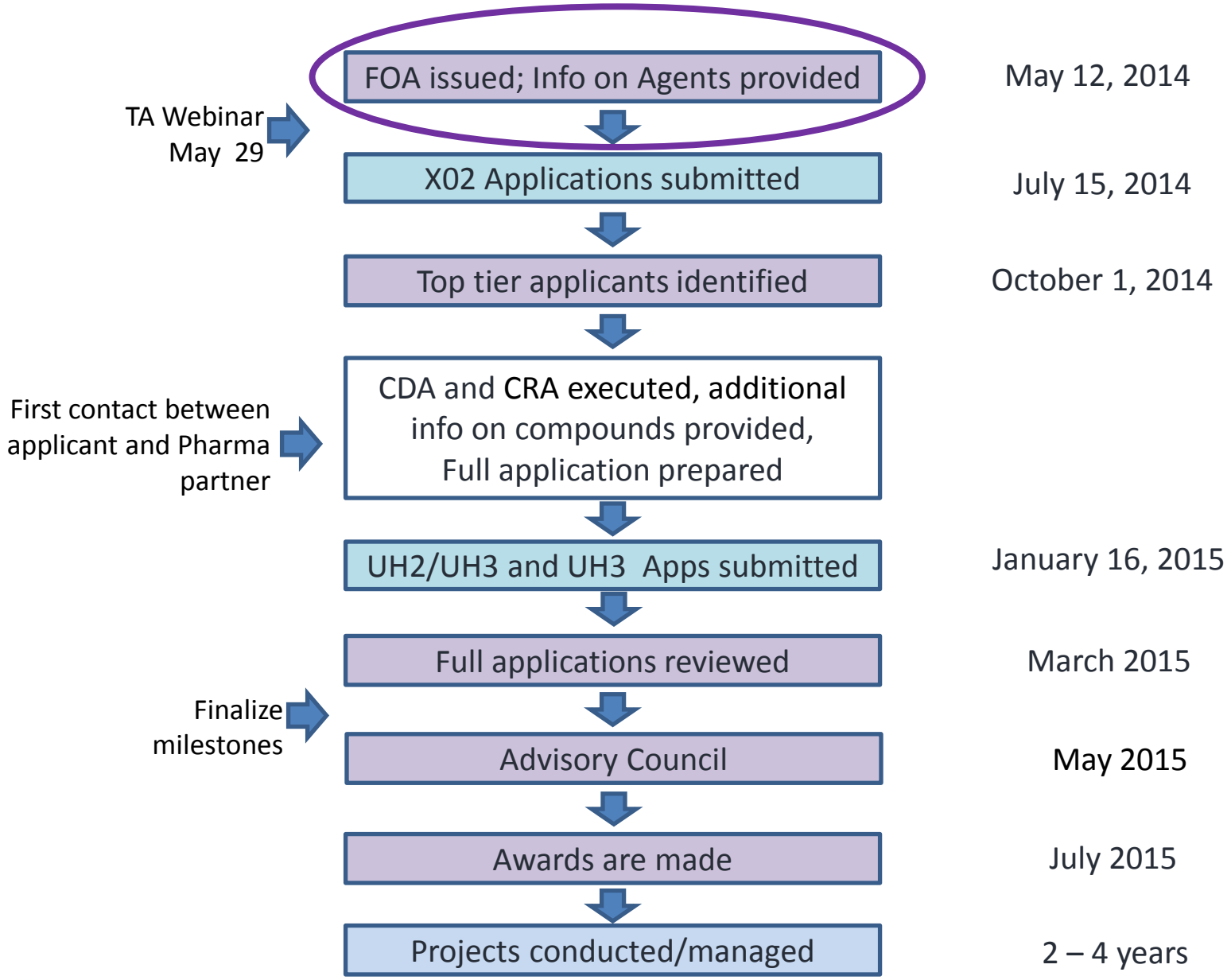

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http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/directory2014.html

Table of Agents for Adult Indications

Code Number & Link to More Information	Mechanism of Action	Original Development Indication(s)	Route of Administration Formulation Available (CNS Penetrant+/-)
RWJ-445380	Cathepsin S Inhibitor	Psoriasis, Rheumatoid Arthritis	Oral
SAR114137	Cathepsin S (CTSS) Inhibitor	Chronic Pain (OA pain, neuropathic pain, chronic low back pain)	Oral (might be CNS penetrant)
CNTO 888 Carlumab	Chemokine (C-C motif) Ligand 2 (CCL2) Selective human IgG1 Kappa Monoclonal Antibody	Idiopathic Pulmonary Fibrosis	Intravenous (i.v.) (No)
AZD9291	Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Sensitizing and T790M Resistance Mutations Inhibitor	Non-Small Cell Lung ancer (NSCLC)	Oral (Unknown)
SAR110894	Histamine H3 Receptor Antagonist	Symptomatic treatment of Alzheimer's disease	Oral (Yes)
JNJ-31001074 Bavisant	Histamine Type 3 (H3) Receptor Antagonist	Attention Deficit Hyperactivity Disorder	Oral (Yes)
AZD4017	11-Beta Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1) Inhibitor	Diabetes	Oral (Low)
AZD2014	Mammalian Target of Rapamycin (mTOR) Serine/ Threonine Kinase (dual TORC1 and TORC2) Inhibitor	Solid Tumors	Oral (Unknown)

AstraZeneca	AZD2624
Mechanism of Action	Neurokinin-3 receptor, tachykinin receptor 3 (NK3R; TACR3) antagonist; http://www.ncbi.nlm.nih.gov/gene/6870
Overview	AZD2624 is a potent human NK3R antagonist (K_i of 2 nM; calcium flux IC_{50} of 2.6 nM) with >100-fold selectivity over a panel of 184 other receptors, enzymes and ion channels, including NK2R, NK1R and cholecystokinin 2 receptor (CCK2R). The major human metabolite has only slightly weaker human NK3R antagonist potency (calcium flux IC_{50} of 9.0 nM) with selectivity of >10-fold to NK2R. In gerbils, AZD2624 significantly reversed senktide-induced suppression of locomotor activity by both the intraperitoneal and oral routes with ED_{50} values of 0.48 mg/kg and 1.1 mg/kg, respectively. From consideration of in vitro data and in vivo findings in pre-clinical species, AZD2624 is anticipated to demonstrate low CNS exposure at therapeutic doses.
Safety/Tolerability	AZD2624 has been administered orally in single doses up to 80 mg and multiple doses up to 30 mg twice daily (BID) for 7 days or 40 mg every day (QD) for 6 days in healthy volunteers, and also at 40 mg QD for 28 days in schizophrenia patients. The most common AEs in excess of placebo were headache, abdominal discomfort, eye pain, somnolence and upper respiratory tract infection, all mild to moderate, as well as an apparent primary pharmacology, mechanism-based reduction in serum testosterone in males. Preclinical studies of up to 3 months duration have been performed.
Additional Information	Clinically significant, transient, reversible, and asymptomatic reductions in total serum testosterone have been noted at doses/exposures estimated for primary target engagement in male subjects. Testosterone and LH lowering have also been seen with other NK3R antagonists (talnetant [GlaxoSmithKline] and osanetant [Sanofi]; ref). NK3R antagonism–induced lowering of hypothalamic GnRH pulsatility is the suspected cause. The effect of AZD2624 on female gonadal hormones is not known. AZD2624 at 40 mg QD for 28 days was not found to be effective in schizophrenia patients.
Suitable for and Exclusions	Until further data are available, AZD2624 is considered not suitable for administration in pregnant or lactating women or in women who are trying to conceive. Conception while on treatment must be avoided. Since interaction with the metabolism of oral contraceptives cannot be excluded, trial protocol will require the use of alternative highly effective forms of contraception. Monitoring for reductions in total serum testosterone should be included in male patients. Suitable for study in indications, sub-populations and/or endpoints that are manifestly distinct from those previously studied for this compound or mechanism of action.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD2624&Search=Search
Additional Characteristics: CNS Penetrance/Pediatric Diseases	AZD2624 has low CNS penetration and, thus, is probably not suitable for a CNS indication. Pediatric disease projects cannot be supported at this time.
Publications	http://www.ncbi.nlm.nih.gov/pubmed/20937004

Once an Agent is selected

- Investigators are strongly encouraged to consult with the appropriate office (such as the Technology Transfer office) within their organization to consider the institution's willingness to agree to the conditions in the appropriate CDA and CRA for the selected Agent.

Template Agreements

CONFIDENTIAL DISCLOSURE AGREEMENTS

- AstraZeneca
- Janssen Research & Development, L.L.C.
- Pfizer Inc.
- Sanofi

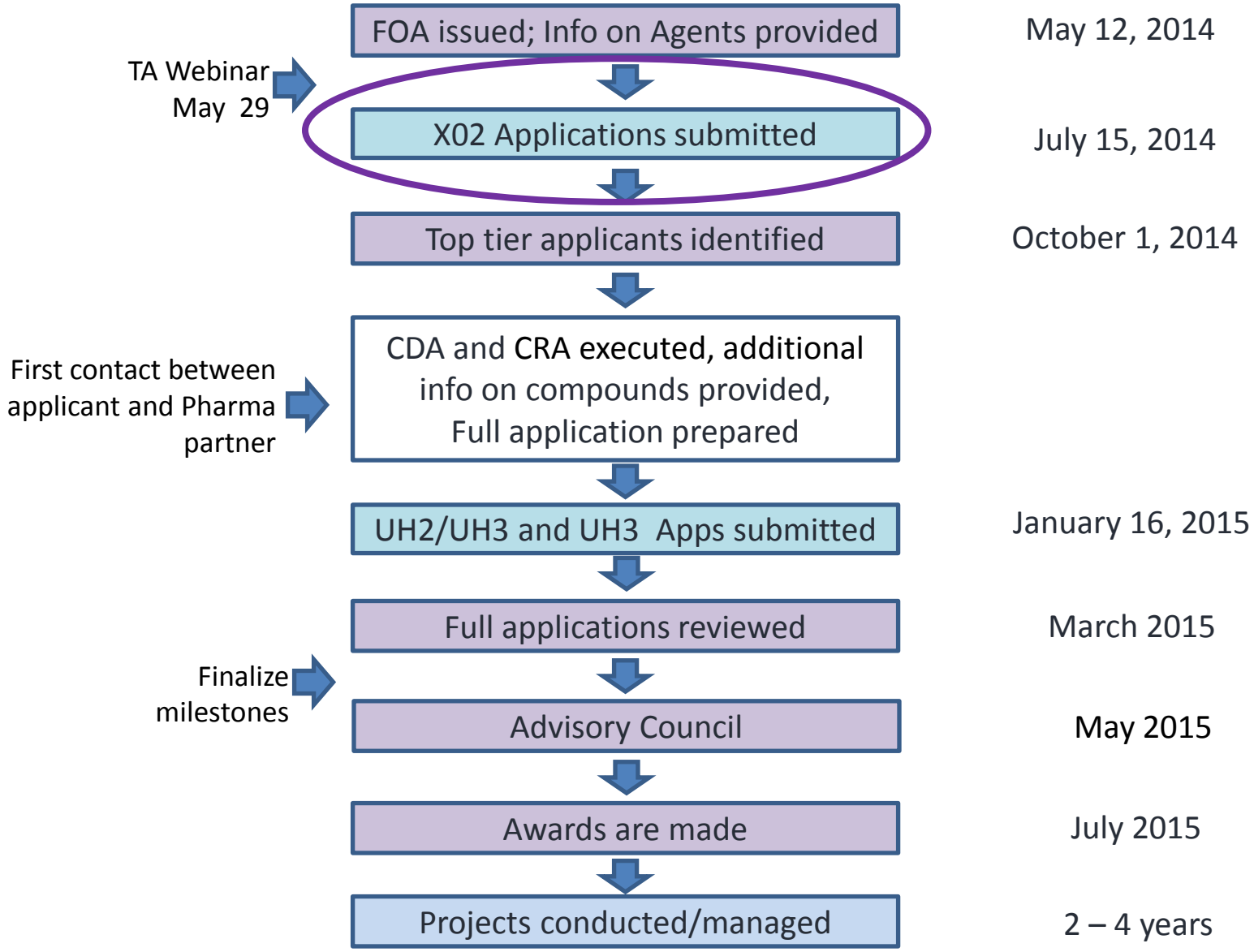
COLLABORATIVE RESEARCH AGREEMENTS

- AstraZeneca
- Janssen Research & Development, L.L.C.
- Pfizer Inc.
- Sanofi

http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/agreements2014.html

Letter of Intent (LOI)

- Assists NIH with preparing for review of applications
- NIH requests submission of LOI's by June 15, 2014
- Not binding
- Not required
- Will not be provided to reviewers
- Will not factor into review of the application
- The LOI should be sent by email to:
  - Therapeutics.Discovery@nih.gov



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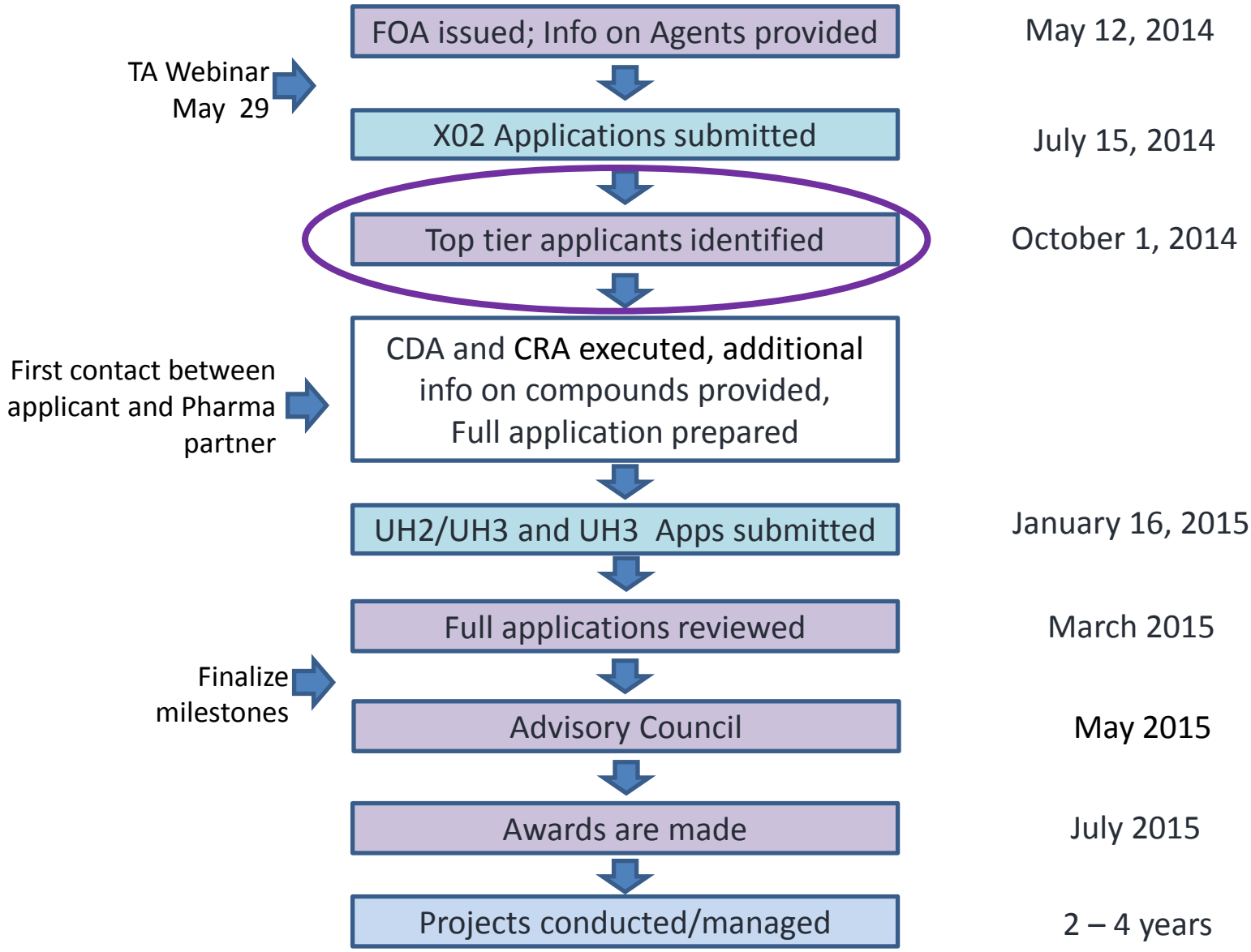
Structure of Research Strategy for X02 Pre-Applications

- Specific Aims - 1 page: delineate Aims for UH2 stage, if applicable, and UH3 stage
- Research Strategy - up to 4 pages
  - Background and Significance
  - Preliminary Studies
  - Approach
  - Administration and Management

A strong application will be supported by scientific evidence that modulation of the Agent's target will have a positive impact on the disease/condition.

The following should NOT be included in the X02 pre-application

- Resource Sharing Plan
- Human Subjects section – even if human subjects are involved
- Vertebrate Animal section – even if animals are involved
- Consortium/Contractual arrangements attachment
- Budget
- Appendices



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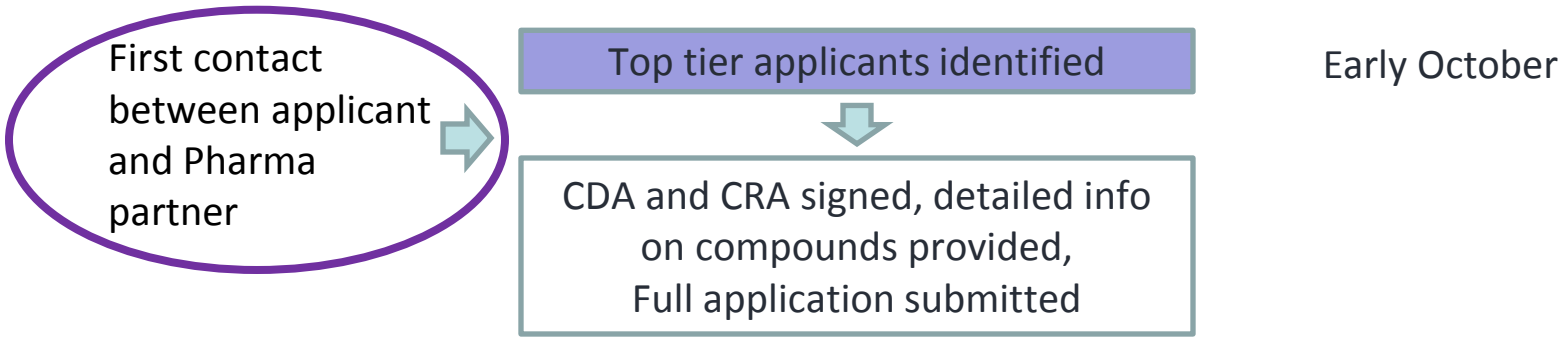
Evaluation of X02 pre-applications

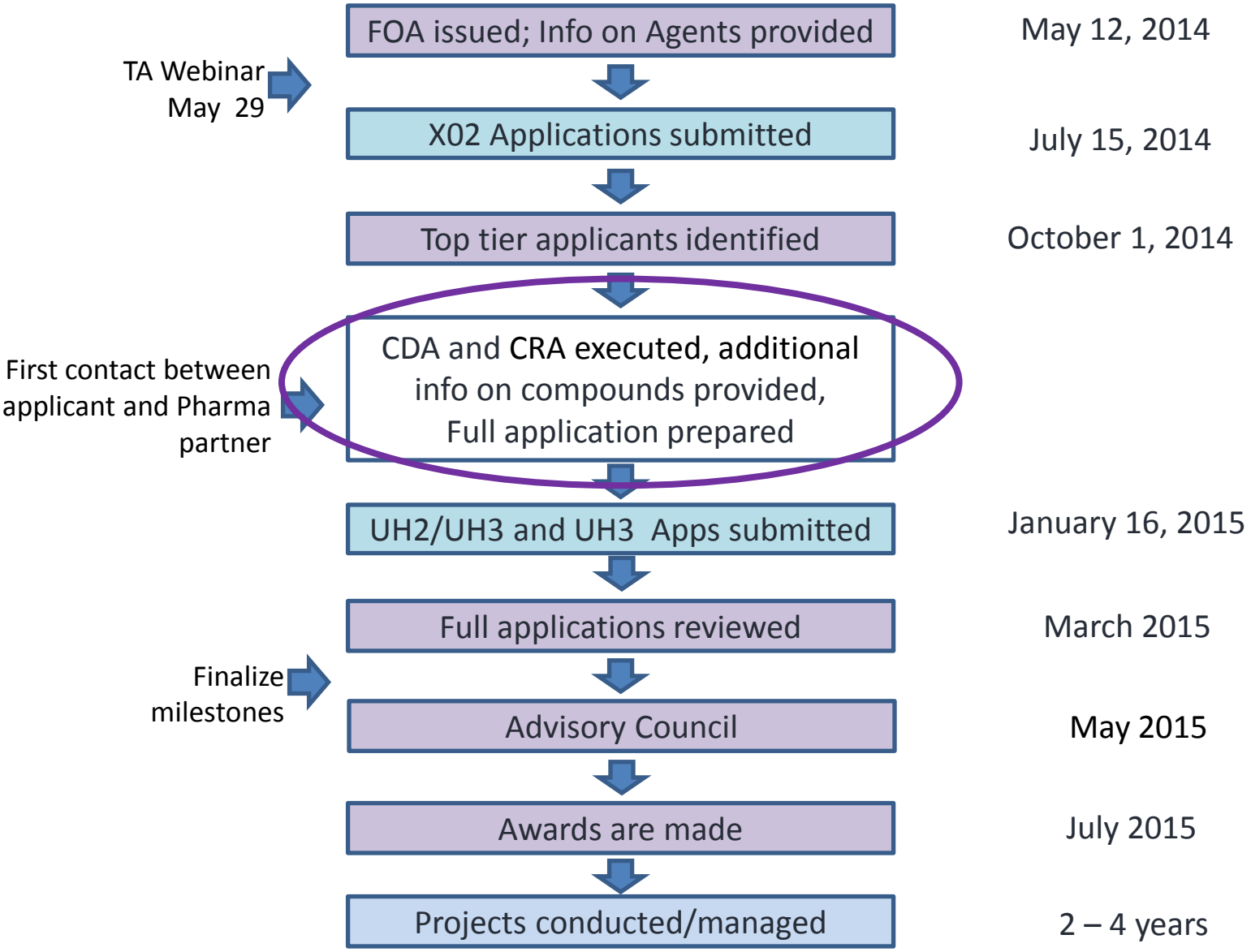
- Review administered by NIH
- External panel of experts
- Pharmaceutical partner personnel do not participate in the review
- Applications will be scored
- Summary statements will be made available

Top tier applications identified

- Successful applicants will receive notification of the contingent* opportunity to submit a UH2/UH3 or UH3
- Notification will include contact information for the pharmaceutical partner identified in X02 application



*UH2/UH3 or UH3 application submission is contingent upon Applicant having access to the Agent.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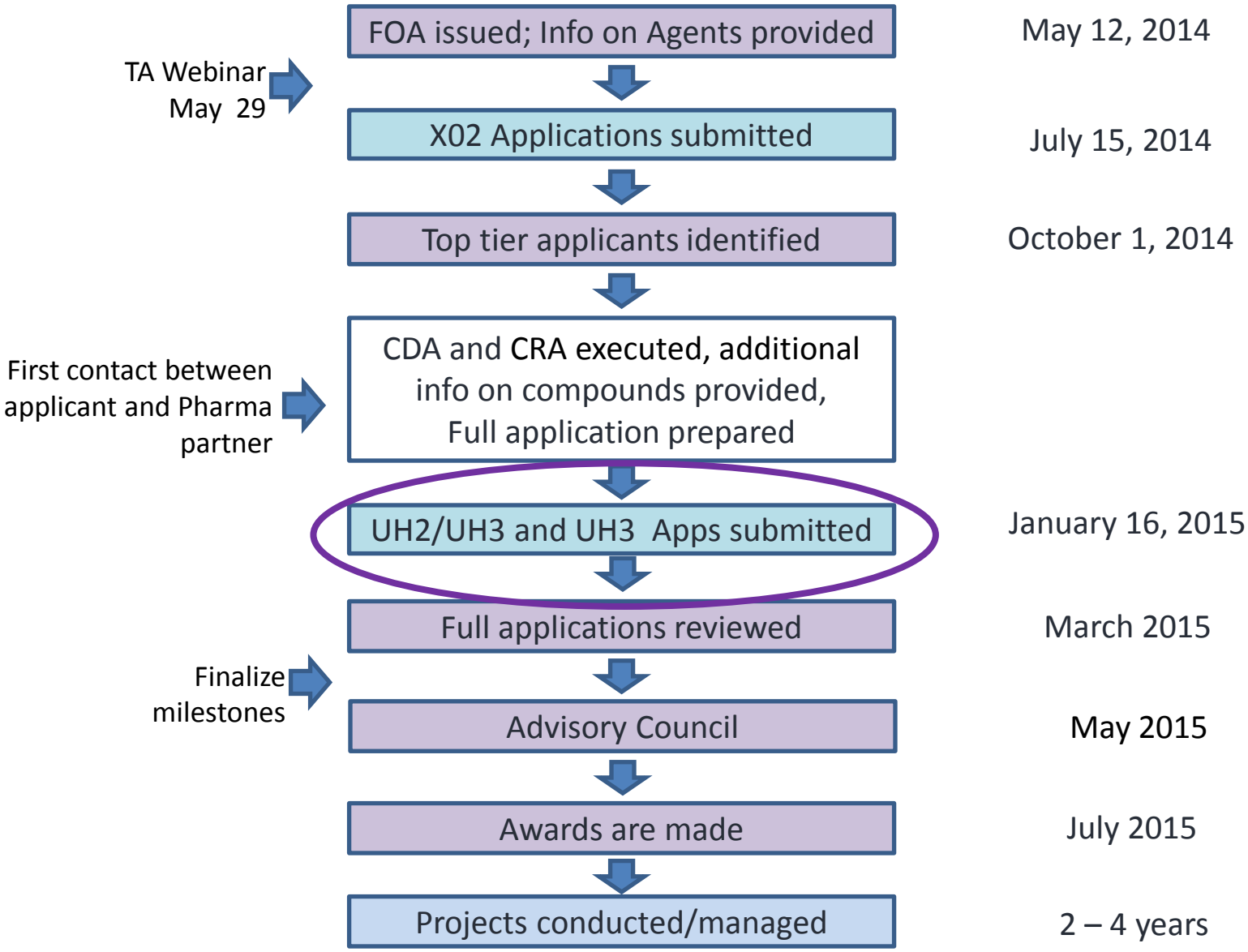
Confidential Disclosure Agreement (CDA)

- Executed by the applicant institution authorized signing official
- Executed by pharmaceutical company authorized signing official
- Enables the parties to share confidential and proprietary information about the Agent in order to prepare a full UH application for PAR-14-210, PAR-14-211, or PAR-14-212

Collaborative Research Agreement

- Must be signed before the UH2/UH3 or UH3 application is submitted to the NIH
- A letter of support from the pharmaceutical company partner must be included in the UH2/UH3 or UH3 application documenting that the applicant(s) will have access to the Agent and associated data needed for conducting the proposed pre-clinical and/or clinical studies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UH2/UH3 vs UH3 Application

- The decision of whether to submit a UH2/UH3 or UH3 application should be made by the investigators based on the existing data on the Agent as it relates to the proposed new therapeutic use
- UH2/UH3 supports a two-stage approach in adults, including feasibility studies (pre-clinical or Phase 1b trials; up to 1 year) prior to a Phase 2a trial
- UH2/UH3 for pediatric indications supports a two-stage approach, including a longer feasibility stage (up to 2 years) to cover required pre-clinical toxicity studies
- UH3 supports implementation of Phase 2a trials (no feasibility studies needed)

Phase 1a, 1b and Phase 2a definitions for this program

- Phase 1a trials are defined as initial studies in healthy adult volunteer subjects or the pediatric rare disease subjects; or other initial studies (using the proposed pediatric formulation) to determine the metabolic and pharmacological actions and the side effects (including those associated with increasing drug doses, or drug-drug interactions in cases where the agents will be tested as adjunctive treatment), as required by the FDA.
- Phase 1b trials are defined as studies usually conducted in the target patient population to establish feasibility (e.g., target engagement, PD/PK, initial dosing of the Agent) prior to a Phase 2a trial.
- Phase 2a clinical trials provide data on the relationship of dosing and response for the particular intended use, including trials on the impact of dose ranging on safety, biomarkers, and proof of concept; trials are typically 150 subjects or less for adults.

Structure of Research Strategy for UH2/UH3 Applications up to 12 pages

- UH2
  - Background and Significance
  - Preliminary Studies
  - Approach for the UH2
  - Milestones and Timeline for the UH2
- UH3
  - Approach for UH3
  - Milestones and Timeline for UH3
  - Future Plans

A strong application will be supported by scientific evidence that modulation of the Agent's target will have a positive impact on the disease/condition.

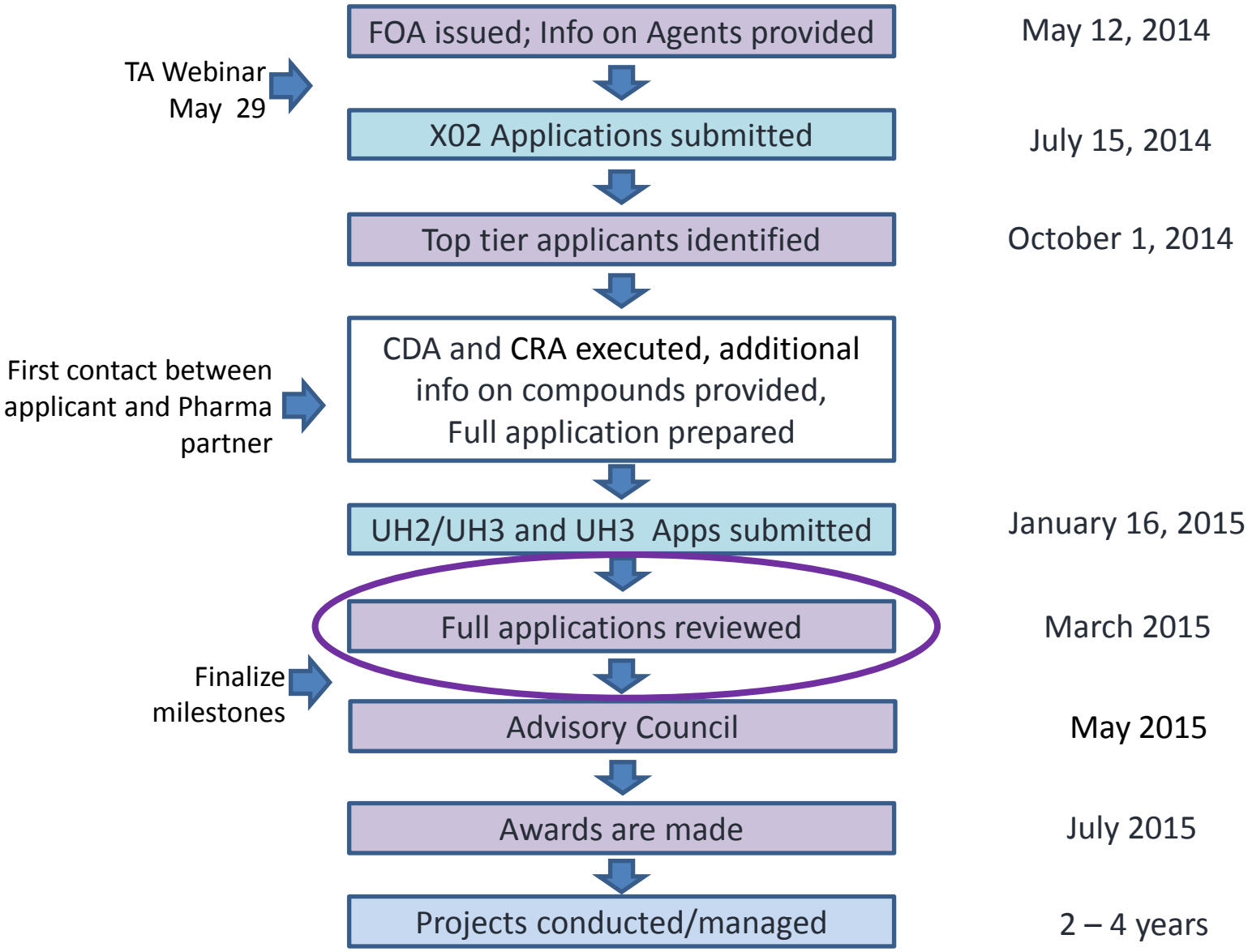
Structure of Research Strategy for UH3 Applications – up to 12 pages

- Background and Significance
- Preliminary Studies
- Approach
- Milestones and Timeline
- Future Plans

A strong application will be supported by scientific evidence that modulation of the Agent's target will have a positive impact on the disease/condition.

Milestones and Timeline

- Included within the 12-page Research Strategy
- Will be part of the Additional Review Criteria
- Will factor into the overall score
- Additional guidance is provided in the FOA



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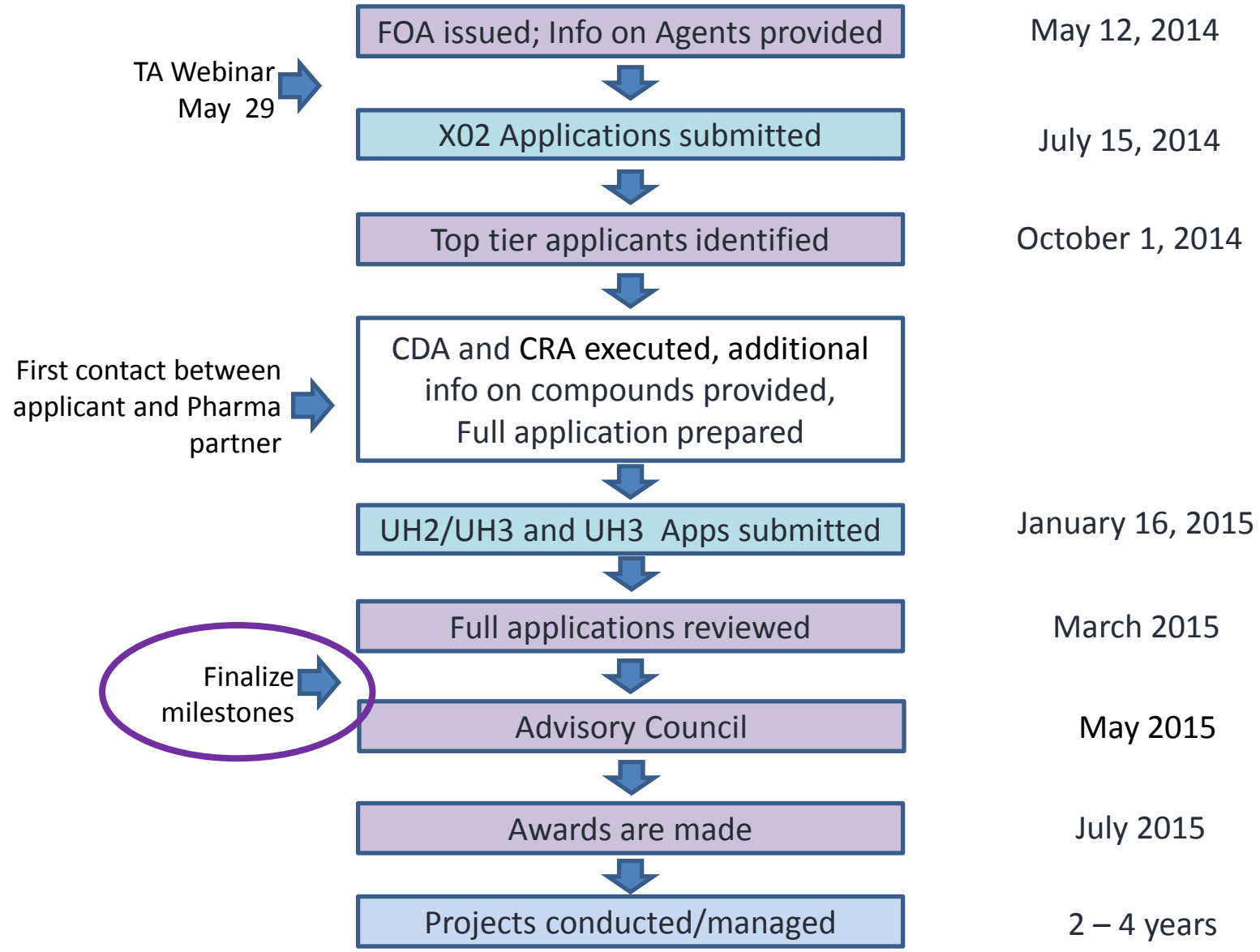
Review of the UH2/UH3 and UH3 applications

- Pharmaceutical partners will not be represented on the panel
- Applications will receive a score and summary statement
- *Additional Review Criteria* including Milestone and Timeline will be factored into the overall score of an application



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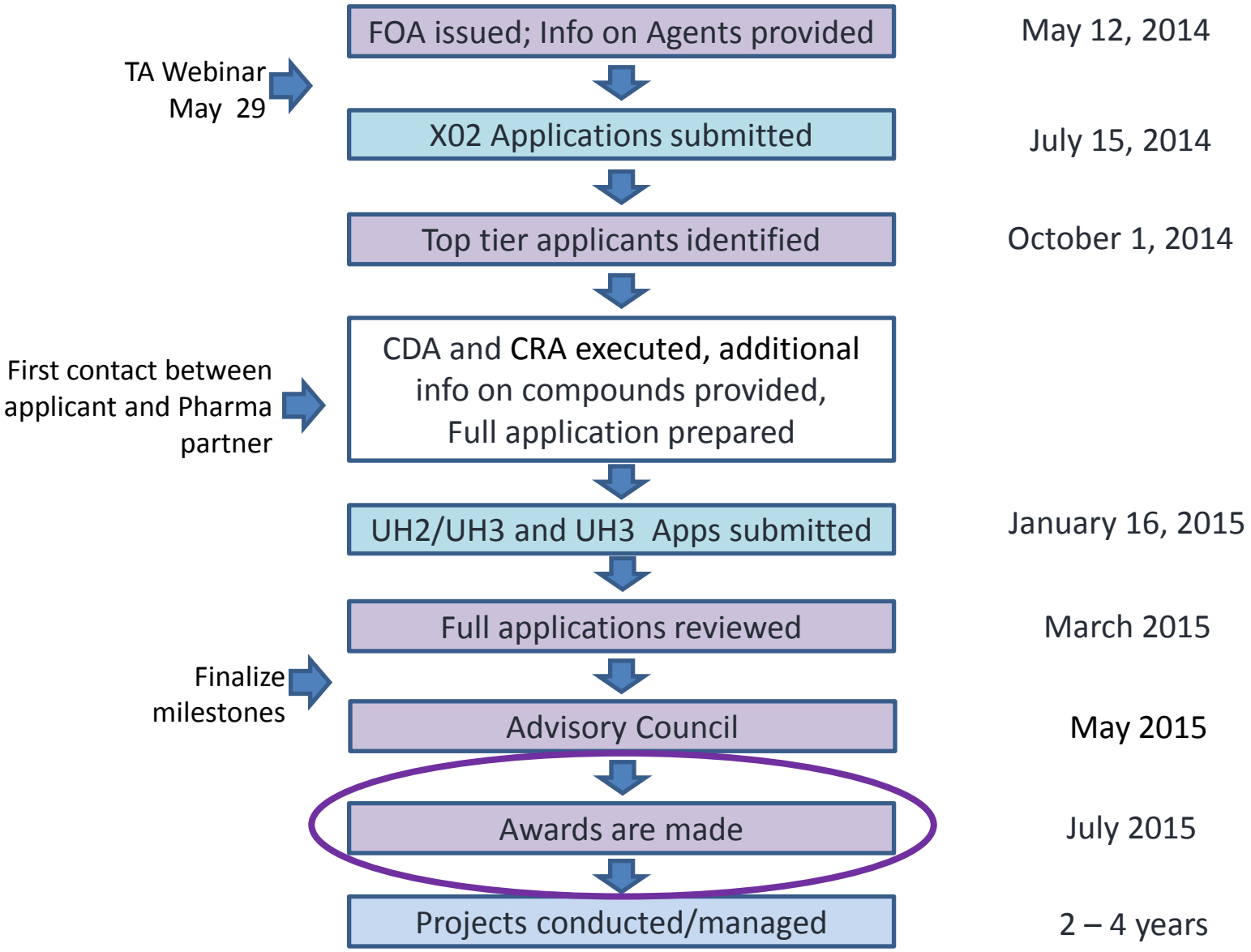
Staged (UH2/UH3)

- Prior to funding an application, the Program Official will contact the applicant to discuss the proposed UH2 and UH3 milestones and potential changes suggested by NIH staff or the NIH review panel. The Program Official and the applicant will negotiate and agree on a final set of approved UH2 milestones, which will be specified in the Notice of Award. These milestones will be the basis for judging the successful completion of the work proposed in the UH2 stage and progress towards interim milestones in the UH3 stage.
- The Program Official will be responsible for determining if the awardee has met the milestones and feasibility requirements for transition of the project from the UH2 to the UH3 stage.
- The Program Official reserves the right to obtain periodic external peer review and recommend reviewers for an assessment of progress and achievement of milestones.



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NIH Cooperative Agreements "U" Awards

- Awardee has primary responsibility for the project
- NIH Project Scientist will have substantial involvement, including participation in weekly project meetings
- NIH Program Official will be responsible for normal scientific and programmatic stewardship of the award
- Each project will have a Steering Committee (SC)
  - PD/PI(s) and designated key personnel
  - Pharma collaborator, *ex officio*
  - NIH Project Scientist(s) and Program Official
  - External Scientists (invited by the PD/PI in consultation with other SC members)

Frequently asked questions

Should I contact the pharmaceutical company before submitting my X02?

No. Applicants should not contact the pharmaceutical companies before the X02 is submitted. Applicants whose X02 pre-applications are identified as being highly meritorious and relevant to NIH program priorities will be notified of the opportunity to submit UH2/UH3 or UH3 applications. The notification will indicate the appropriate pharmaceutical company contact. However, applicants should work with their institution in advance to discuss the conditions in the collaborative research agreement for the selected agent prior to submitting the X02 pre-application.

There is more than one agent with the same target/mechanism of action on tables found on the Industry-Provided Agents page. Do I need to choose one in particular when I submit my X02 application?

No. In some cases, there will be sufficient information in the one-page summary charts for applicants to choose the most appropriate agent for the proposed study. In cases where the information provided on the NCATS website is not sufficient for an applicant to choose, he or she may simply identify the target/mechanism of action in the X02 application. X02 applicants who are notified of the opportunity to submit UH2/UH3 or UH3 applications will receive company contact information to execute a confidential disclosure agreement with agent providers and obtain more information on the agents. To be responsive, the UH2/UH3 or UH3 application must identify a single agent.

Could investigators apply separately for each molecule Agent on the list?

Applicants may submit more than one application, provided that each application is scientifically distinct. However, applicants should focus on one Agent to develop biological evidence for the proposed.

Is this funding opportunity limited to the agents provided through the New Therapeutic Uses program, or can investigators propose other agents? If investigators have an agent they believe may have a new use but is not listed in the industry-provided agents tables for this program, can they apply?

This funding opportunity is limited to those agents provided by pharmaceutical company collaborators for the New Therapeutic Uses program through a Memorandum of Understanding with NIH. The program will not provide support for agents not listed in the tables on the Industry-Provided Agents page. We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Institute or Center contacts can assist in directing investigators to other FOAs to propose new therapeutic uses of other agents that might be of interest in specific disease areas.

Are proposed new uses for this program limited to stand-alone interventions?

No. The program supports clinical studies/trials to develop new uses of the agents as stand-alone interventions or as add-ons to current treatments if there is no evidence of drug-to-drug interactions with the standard-of-care treatment.

Can an investigator submit an application requesting the collection of agents for pre-clinical studies, including screening?

No. This program does not support screening of the agents. The primary focus of applications should be on clincial trials (Phases Ib and IIa). If proposed, pre-clincial studies should be justified and tied to go/no-go decisions to test the agent in the patient population.

How do I include the background information on the Agent(s) that will be subject of the X02 pre-application?

Visit the Table of Agents on the NCATS website. The code for each Agent is hyperlinked to a chart describing the Agent including Mechanism of Action, Overview, Safety/Tolerability, Additional Information, Suitable for and Exclusions, Clinical Trials, Additional Characteristics, and Publications. Save a copy of the chart as a PDF file entitled "Agent Information". Attach this file to the Other Project Information of the SF424(R&R).

Can investigators from small businesses and for-profit organizations apply for funding?

Yes. Small businesses and for-profit organizations with more than 51 percent U.S. ownership are eligible to apply.

Can an NIH-funded academic researcher and a biotech company collaborate to apply for the New Therapeutic Uses program?

Yes. NIH encourages scientific collaboration to leverage additional expertise and resources.

Are NIH IRP investigators eligible to apply for these funding opportunities?

Yes. NIH IRP investigators can apply as program director(s)/principal investigator(s) (PDs/PIs), as multiple PDs/PIs in conjunction with extramural investigators, or as collaborators with extramural academic or biotechnology company investigators, pending the availability of their respective Institute's or Center's intramural funds to support the project. IRP investigators and laboratories cannot request extramural funds. An official letter from the IRP applicant's scientific director that indicates approval of the IRP scientist's role as PD/PI or as collaborator in the project must be included as a letter of support in the submission of the X02 pre-application.

Does the IRP program director/principal investigator need to be a tenured/tenure-track investigator?

Yes. Tenure-track investigators can apply if they will be at NIH for the full duration of the project; they should have approximately four years left at NIH (or five years if a pediatric trial will be proposed) at the time of application because the submission, review and award process can take up to one year. Postdoctoral fellows, staff scientists and others are not eligible to apply.

Are these agents approved by the Food and Drug Administration (FDA) for clinical use?

None of the agents used in these studies are FDA-approved drugs. However, before any agents will be used in clinical studies, each investigator will file an investigator-sponsored Investigational New Drug application with the FDA to conduct the proposed clinical trials.

What are the agent selection criteria?

Agents selected for the program have advanced to clinical studies, and they have a safety profile, which allows further clinical investigation for other potential therapeutic uses. The mechanism of action for each compound is known, and pharmacokinetics is suitable for exploring the mechanism for a new indication.

Can foreign applicants or companies apply to the program?

No. Foreign investigators and institutions are not eligible to apply. However, they may participate as subcontractors of an awarded U.S. institution or investigator. Foreign components, as defined in the NIH Grants Policy Statement, are allowed.

If I have a dual appointment with NIH and an extramural research organization, which organization should I use as the applicant organization?

Choice of applicant institution depends on a variety of factors, including but not limited to the duration of the appointments, the specific terms of each appointment, the availability of funds at the NIH laboratory, the available resources of each organization and many other individual factors.

Are applicants required to use the template confidential disclosure agreements (CDAs) and collaborative research agreements (CRAs) posted on the NCATS website?

In the X02 pre-application, applicants must include a letter of support from the appropriate institutional official confirming the institution's willingness to engage in the necessary negotiations with the pharmaceutical company. One of the barriers encountered in moving forward projects that involve the private sector and the academic sector or other collaborators is the time it takes to execute a CRA or equivalent document. In recognition of this barrier, template agreements have been developed to streamline interactions among the parties for the program. It is anticipated that applicants will use the agreements.

X02 applicants should consider their willingness and the willingness of their institution to agree to the conditions in the appropriate CRA for the selected agent prior to submitting a pre-application. Investigators should work with the appropriate office within their organization to finalize the terms and conditions of the CDA and CRA for the selected agent prior to submission of a UH2/UH3 or UH3 application.

Use of the template agreements is not required. However, UH2/UH3 and UH3 applications submitted without evidence of access to and the ability to work with the agents, such as evidence that a CRA or equivalent document has been executed, will be deemed incomplete and returned to the applicant without review.

Are there any limitations on the use of agents in pediatric populations?

Yes. In general, pediatric populations to be considered for this funding opportunity announcement (FOA) refer to disease populations for which there is no adult equivalent and thus no adult population in which the drug could be tested prior to testing it in children. However, trials in pediatric or juvenile populations for indications that also have an adult population (e.g., type 2 diabetes, autism, osteoarthritis) may be considered if there is a strong scientific rationale that justifies why Phase IIa trials in the pediatric population are required even though an adult patient population exists (e.g., the target in the pediatric population may differ from that in the adult or treatment of children may reduce progression or severity of the disease).

Agents that the pharmaceutical companies will consider for use in pediatric populations are listed in the Table of Agents for Pediatric Indications. Applicants must click on the agent code number in the first column of the table to obtain more detailed agent information. To determine the type(s) of pediatric diseases the pharmaceutical company will consider (e.g., only trials in pediatric populations for which there is no adult population; trials for diseases/conditions that have a pediatric and adult population, if the trials in a pediatric population are scientifically justified), open the agent of interest and refer to the "Additional Characteristics" row. Applicants exploring therapies for diseases that occur in children and adults should consider applying in response to one of the companion UH2/UH3 or UH3 FOAs focusing on adult populations.

What types of studies are acceptable for pediatric indications?

Applicants should refer to the Table of Agents for Pediatric Indications to determine if the agent will be considered by the pharmaceutical company for pediatric use. After clicking on the agent of choice in the first column of the table, refer to the "Additional Characteristics" row of the more detailed agent information chart. This row provides information on the types of pediatric indications that the pharmaceutical company will consider (e.g., only trials in pediatric populations for which there is no adult population; trials for diseases/conditions that have a pediatric and adult population, if the trials in a pediatric population are scientifically justified).

Applicants must provide NIH with documentation of access to the agent and associated data needed for conducting the proposed pre-clinical studies and pediatric clinical trials and for filing an investigator-sponsored Investigational New Drug application to conduct the proposed clinical trials in a UH2/UH3 application (e.g., letter from the pharmaceutical company providing access to the agent for the indicated use).

Program Contacts

- **National Center for Advancing Translational Sciences (Main Contact)**
  Christine Colvis, 301-451-3903
  therapeuticsdiscovery@mail.nih.gov

- **Technology Transfer Contact**
  Lili Portilla, 301-217-4679

- **National Institute of Mental Health**
  Linda Brady Jill Heemskerk

- **National Eye Institute**
  George McKie

- **National Institute on Deafness and Other Communication Disorders**
  Janet Cyr

- **National Institute on Drug Abuse**
  Ivan Montoya Jane Acri

- **National Heart Lung and Blood Institute**
  John W Thomas Patricia J Noel
  Simhan Danthi

- **National Institute on Aging**
  Larry Refolo

- **National Institute on Alcohol Abuse and Alcoholism**
  Joanne Fertig Mark Egli

- **National Cancer Institute**
  Barbara Mroczkowski

- **National Institute of Neurological Disorders and Stroke**
  Patricia Walicke

- **National Institute of Child Health and Human Development**
  Anne Zajicek

- **National Institute of Dental and Craniofacial Research**
  R. Dwayne Lunsford

- **Food and Drug Administration**
  Katherine Needleman

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